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EFFECT OF CAFFEINE ON BILE AND PANCREATIC JUICE SECRETION

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16. Abstract
A series of experiments on rats demonstrate that caffeine alone has very little effect on bile secretion, but that it does produce a 100% increase in pancreatic flow, although the protein content of the pancreatic juice does not increase proportionately. Several possible explanations for this effect are offered, but it is not yet possible to draw any definite conclusions.

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EFFECT OF CAFFEINE ON BILE AND PANCREATIC JUICE SECRETION

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Some people state that their digestion is better when they /515* drinkaa fluid with a base of coffee, tea, maté, etc., during or after meals. Others consider themselves unable to drink fluids of this type due to digestive problems.

A number of studies have dealt with the effect of caffeine on gastric secretion; this has not been the case, however, for pancreatic and bile secretion.

This report contains the results of an experiment on the effects of caffeine in rats.

Technique

The experimental animal used was the male Wistar rat[1], weighing 275 to 350 g.

The animals were anesthetized by injection of a 50% urethane solution at a rate of 0.25 ml/100 g body weight; a single dose was injected into the thight.

Using a technique described elsewhere (Debray, 1962 a [5]), we collected the bile and the pancreatic juice by means of two

[1] CF strain, CNRS [Centre national de recherche scientifique; National Scientific Research Center], Gif-sur-Yvette.

*Numbers in the margin indicate pagination in the foreign text.

catheters. Measurements were performed, first, for the pancreatic juice: on output, protein concentration and output (providing some idea of the total enzyme content) and amylase concentration and output; and second, for the bile: on bile output and the bilirubin concentration and output.

For the measurements, the first two drops of pancreatic juice were set aside since they were contaminated with bile. Subsequently one drop of pancreatic juice was sampled alternately for the amylase measurements and one drop for the protein measurements.

Each time a pancreatic tube was removed for the amylase measurements, the bile collection tube was returned to position. The weighed tubes were kept under refrigeration until measurement. The pancreatic juice protein measurements were made on one drop (approximately 10 mg) by the Lowry method [17]. It was possible to compute the output on the basis of the protein concentration and the weight of the juice collected.

The amylase was measured by the modified Somogyi method (Debray, 1962 [5]). The results were arbitrarily expressed as the quantity of reducing sugar yielded in the form of glucose which /516
was released by the test sample; one unit corresponded to the release of 10 γ glucose in the reaction tube. Bilirubin was measured by the Jendrassik method [16].

Caffeine was administered by the slow intravenous administration of Codex solute (caffeine 0.25; sodium benzoate 0.35; water S.Q. for 1 ml) in a dose of 0.05 g caffeine per kilogram. After pancreatic secretion had begun, a period of one hour was allowed to elapse so as to obtain a base output value. At the end of this interval ("time zero"), the caffeine was injected into the femoral vein. Measurements were then made after one, two and three hours. The results were expressed as follows:

-- pancreatic output in drops per hour;
-- protein concentration in grams per thousand;
-- protein output in micrograms per minute;
-- amylase concentration in units per milligram;
-- amylase output in units per minute;
-- bile output in drops per ten minutes and per hour;
-- bilirubin concentration in milligrams per thousand grams;
-- bilirubin output in micrograms per ten minutes.

The differences between the figures obtained before and after injection were used to reduce the differences between animals. The conventional notation Δ (= difference) was used, followed by a subscript giving the time in minutes. The Δ_{60} pancreatic output was thus obtained (difference between pancreatic output during the 60 min following and the 60 min preceding the injection of caffeine), etc.

Ten control rats were used, 14 rats for caffeine administration alone, 11 for caffeine after atropine, 7 for caffeine after pyloric ligature and 10 for atropine alone.

A statistical analysis was performed on the results, using variance analysis methods.

Results

These are given in Tables 1 through 3.

1. Effect of Caffeine Alone

(a) Pancreatic juice. The juice output was heavily increased (by 90% the first hour, 90% the second hour, and 95% the third hour); this was a very lasting phenomenon. Protein concentration was conjointly decreased, and as a result there was virtually no variation in the total pancreatic protein output.

Considering the amylase activity alone, however, there was an increase in output of approximately 50% during the first hour and 30% the third hour. Given the considerable scattering of individual values, the variation was significant only during the first hour.

(b) Bile. Caffeine demonstrated a slight choleretic effect which did not occur absolutely immediately, since it could not be detected during the first 10 min, and which was appreciable only one hour after injection. Thus prevention of the usual decrease in output was involved, rather than severe hyperchloresis (order of magnitude approximately 5%).

TABLE 1. EFFECT OF CAFFEINE (50 mg/kg) ON OUTPUT AND COMPOSITION OF PANCREATIC JUICE /517

	Controls	Caffeine	P*
Δ 60 pancreatic output (drops/hr)	-0.08	3.68	0.001
Pancreatic output (drops/hr)			
1 hr before	3.75	3.80	N.S.
1 hr after	3.12	7.19	0.001
2 hrs after	3.25	7.23	0.001
3 hrs after	3.40	7.36	0.001
Protein concentration (g/100)			
Δ 60	-1.82	-6.30	0.01
Δ 120	1.18	-9.11	0.01
Δ 180	0.36	-8.28	0.001
Protein output (μg/min)			
Δ 60	-1.48	1.82	N.S.
Δ 120	-0.94	2.42	N.S.
Δ 180	-0.57	1.45	N.S.
Amylase concentration (U/mg)			
Δ 60	-1.23	-0.82	N.S.
Δ 120	-0.65	-1.49	N.S.
Δ 180	-0.30	-1.90	N.S.
Amylase output (U/min)			
Δ 60	-1.23	2.07	0.001
Δ 120	-0.54	1.30	N.S.
Δ 180	-0.37	-0.27	N.S.

*P = significance threshold for test of difference between groups.

TABLE 2. EFFECT OF CAFFEINE (50 mg/kg) ON BILE OUTPUT AND EXCRETION OF BILIRUBIN

	Controls	Caffeine	P
Bile output			
Δ 10 (drops/10 min)	-0.39	-0.21	N.S.
Δ 60 (drops/hr)	-2.40	0.86	0.001
Δ 120 (drops/hr)	-5.90	-4.15	N.S.
Δ 180 (drops/hr)	-8.50	-5.00	N.S.
Bilirubin concentration (mg/ℓ)			
Δ 60	-8.2	5.4	N.S.
Δ 120	-18.8	18.7	0.05
Δ 180	-12.5	28.0	0.01
Bilirubin output (μg/10 min)			
Δ 60	-1.28	0.53	NNSS.
Δ 120	-3.25	1.26	0.01
Δ 180	-2.96	1.08	N.S.

There appears to be a slight increase in the elimination of bilirubin (variation of approximately 5-10%.

2. Effect of Caffeine After Atropine /518

In this series of experiments, a 60 mg/kg dose of atropine sulfate was administered to the animals intravenously in the form of two doses of 30 mg/kg separated by a 15-minute interval.

Ten minutes after the second atropine injection, caffeine was injected (50 mg/kg) by the same method.

(a) Pancreatic Juice. There was a strong increase in pancreatic juice output over that of the control animals; the increase due to caffeine, however, was decreased by half in response to atropine. The effective period was quite long, since the effects still persisted three hours after the injection of caffeine.

(b) Bile. The effect of caffeine on bile output did not ap-

pear to undergo any serious change in response to the administration of atropine. It is difficult to evaluate this effect, since atropine itself manifests a choleretic effect which we were able to observe by injecting atropine alone.

3. Effect of Atropine

(a) Pancreatic juice. Under the experimental conditions, the injection of 60 mg/kg atropine sulfate in the form of two 30 mg/kg doses separated by a 15 minute interval appeared to have only a very slight effect on pancreatic output. The average output (for ten animals) was 4.22 drops/hr one hour prior to injection, and 3.75, 4.16 and 4.66 drops/hr, one, two and three hours after the first atropine injection, respectively.

(b) Bile. There was an obvious effect on bile output. The figures observed were 2.3 drops/10 min for Δ 10 output, and 30.2, 18.2 and 6.1 drops/hr for the Δ 60, Δ 120, and Δ 180 bile outputs, respectively. The effect was strongest during the hour immediately following the injections: at this point the increase over the base output was approximately 50%.

4. Effect of Caffeine After Ligature of the Pylorus

In this series of experiments, the pylorus was ligated during the test period and caffeine was administered as previously.

(a) Pancreatic juice. The pancreatic juice output was increased in a similar manner to that observed in the rats dosed with atropine, with a tendency, however, towards a greater increase after the second and third hours. During the third hour the increase in output was close to that of the animals given caffeine alone.

(b) Bile. The bile output in animals with ligated pylorus receiving caffeine was increased slightly over the series receiving caffeine alone; Δ 60 bile output of 4.28 drops/hr, as opposed to

0.86 (N.S.), Δ 120 of 1.85 as against -4.15 (0.05). This increase, which was slight and not very significant, might have been due to /519 the pyloric ligature itself: by monitoring a group of seven rats with ligated pylorus for four hours, onee may note a slightly higher average bile output in the rats with ligated pylorus than in the control rats.

TABLE 3. EFFECT OF CAFFEINE ALONE, AFTER ATROPINE AND PYLORIC LIGATURE, ON PANCREATIC SECRETION

	Caffeine Alone	Caffeine After Atropine	P*	Caffeine After Pyloric Ligature	P*
Δ 60 pancreatic output (drops/hr)	33668	1.75	0.01	2.21	0.05
Pancreatic output (drops/hr):					
1 hr before	3.80	3.63	N.S.	3550	N.S.
1 hr after	7.19	5.35	0.05	5.71	0.05
2. hrs after	7.23	6.05	N.S.	6.57	N.S.
3 hrs after	7.36	6.45	N.S.	7.28	N.S.

* P = confidence threshold of differences tests in comparison to the group with caffeine alone.

The findings which have just been described may be summarized as follows:

In the pancreas of rats with anesthetized with urethane, caffeine produces a considerable increase in pancreatic output (at least 90% for three hours). This hypersecretion is primarily aqueous: the protein concentration actually decreases as the flow increases, with the result that the protein output increases only very slightly (with the exception of amylase, whose output increases during the first hour).

The increase in pancreatic flow is only decreased by preliminary

nary injection of atropine. Nor does pyloric ligature hinder the secretagogue effect of caffeine.

With reference to bile, caffeine has a moderate stimulatory effect on secretion and on bilirubin output. Atropine alone has a choleretic effect; it does not check the cholerètic effect of caffeine. Pyloric ligature does not change the effect of caffeine on the bile.

Comments

1. Effect of caffeine on bile secretion. As has been seen, the effect of caffeine on bile secretion is relatively slight. It may perhaps be explained by vasodilation of the hepatic blood vessels, since caffeine is known to increase cardiac output ((Dallemagne, 1961 [3]), and physiologists do hold the opinion that bile output depends on the blood flow in the liver (Wakim, [24], Bizard [1]).

As for the unexpected effect of atropine alone on bile secre- /520
tion in the rat, this appears to require a separate examination elsewhere.

2. Effect of caffeine on pancreatic secretion. The sharpest effect of caffeine is a 100% increase in pancreatic flow in the rat. This is primarily a hydrelatic effect comparable to that of secretin, since there is only a very slight increase in the protein and amylase output. Several mechanisms may be used to explain this effect.

(a) Stimulation of gastric secretion by caffeine. Caffeine is known to produce a very sharp increase in gastric secretion in many animals (cats, rats) and man (Roth, 1944, 1951 [20, 22, 23], Musick [18]). In some countries, especially the U.S., caffeine is even preferred to histamine for stimulation of gastric secretion

in tests.

It is thus reasonable to assume that pancreatic hypersecretion due to caffeine occurs in three stages: (1) gastric hypersecretion; (2) formation of secretagogue pancreatic hormones (secretin, pancreozymine) by the arrival of acidic gastric juice; and (3) humoral pancreatic secretion (Debray, 1962, 1963 [5, 6, 9, 10]).

In our opinion, this explanation is unacceptable for the following two reasons:

-- Pyloric ligature, which prevents acidic juice from reaching the duodenum, changes the pancreatic secretagogue effect only partially.[2]

-- Atropine has only an incomplete effect on the secretory effects of caffeine on the pancreas. Atropine does have a powerful effect on the stomach, however; it considerably decreases the secretion of gastric juice and consequently the secretin-forming effect (Grossman, in Gregory [15], Pfeiffer [19]).

(b) Stimulation of bile secretion. Agents accelerating pancreatic secretion are less numerous than choleretic agents. These two effects may be combined in various ways.

Sodium dehydrocholate increases choleresis with virtually no effect on pancreatic secretion during the first hour after injection (Debray, 1964 [12]). A slight increase in secretion occurs only after some time (two to three hours) and with the use of st

[2] Some investigators acknowledge that secretin may be formed by the pyloric antrum, and the preceding criticism was made with this in mind. However, the extent of antral secretin formation remains to be determined.

heavy doses (200 mg/kg).

2,4,6-trihydroxypropiophenone has further effects on the pancreatic juice and extremely strong effects on the bile (Debray, 1964 [13]).

Caffeine, finally, acts basically on the pancreas, and has very little effect on bile secretion. Its effects on the composition of the bile also differ.

Drug-induced pancreatic hypersecretion is therefore unrelated to drug-induced hyperchloresis.

(c) Direct effect of caffeine on the pancreas. One might /521
wonder whether caffeine might not have an effect on the pancreas in the same way that it has an effect on the kidney: it has been noted that a mercurial diuretic combined with theophylline, that is, the exact substances which affect renal secretion, increase pancreatic secretion by a factor of 3 or 4 (Debray, 1962 [7]). Furthermore, little is known about the mechanics of the action of caffeine on the kidney (De Corral [2]). Dallemagne, 1962 [4], notes that some investigators have used the involvement of tissue fluids to explain the fact that caffeine has a diuretic effect only if there is excess water in the organism. Changes in the circulatory dynamics of the kidney have also been considered; however, caffeine has its effect even if the renal blood flow is kept constant. There are large differences between diuresis and pancreatic secretion, however; in particular, the effects of acetazolamide is a large obstacle in the way of understanding of the pancreatic and renal mechanisms. This inhibitor of carbonic anhydrase reduces pancreatic secretion (Dreiling, 1964 [14]), even though it is a powerful diuretic.

Although it may be stated that caffeine does have a direct

effect on the pancreas, the mechanismsinvolved remains unknown.

To solve this problem, it will primarily be necessary to determine whether other non-diuretic respiratory or cardiac analeptics have an effect on pancreatic secretion.

In any case, this considerable pancreatic secretagogue effect and slight choleretic effect provide at least a partial explanation for the eupeptic effects of caffeine, effects which are well-known to epicures and healthy subjects. It is possible that the conditions surrounding these secretions are different in sick people -- excessive or inadequate secretion -- and that these secretory imbalances may result in the disturbances noted by some patients after drinking fluids which contain caffeine.

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